

SEQUENCE LISTING

<110> Leppla, Stephen H.
 Avallone, Jennifer
 Bugge, Thomas
 Liu, Shi-Hui
 Osorio, Manuel
 The Government of the United States of America
 as represented by The Secretary of the
 Department of Health and Human Services

<120> Activation of Recombinant Diphtheria Toxin Fusion
 Proteins by Specific Proteases Highly Expressed on the
 Surface of Tumor Cells

<130> 015280-478100US

<140> US 10/554,076
 <141> 2005-10-21

<150> US 60/468,577
 <151> 2003-05-06

<150> WO PCT/US04/14306
 <151> 2004-05-06

<160> 30

<170> PatentIn Ver. 2.1

<210> 1
 <211> 1683
 <212> DNA
 <213> Corynebacterium diphtheriae

<220>
 <223> wild type Diphtheria toxin (DT)

<220>
 <221> sig_peptide
 <222> (1)..(75)
 <223> signal sequence

<400> 1
 gtgagcagaa aactgtttgc gtcaatctta ataggggagc tactggggat agggggcccca 60
 ccttcagccc atgcaggcgc tgatgatggt gttgattctt ctaaatcttt tgtgatggaa 120
 aactttttctt cgtaccacgg gactaaacct gggtatgtag attccattca aaaagggtata 180
 caaaagccaa aatctggtac acaaggaaat tatgacgatg attggaaagg gttttatagt 240
 accgacaata aatacgacgc tgcgggatac tctgtagata atgaaaaccc gctctctgga 300
 aaagctggag gcgtgggtcaa agtgacgtat ccaggactga cgaagggttct cgcactaaaa 360
 gtggataatg ccgaaactat taagaaagag ttaggtttta gtctcactga accgttgatg 420
 gagcaagtgc gaacggaaga gtttatcaaa aggttcggtg atggtgcttc gcgtgtagtg 480
 ctcagccttc ccttcgctga ggggagttct agcgttgaat atattaataa ctgggaacag 540
 gcgaaagcgt taagcgtaga acttgagatt aattttgaaa cccgtggaaa acgtggccaa 600
 gatgcgatgt atgagtatat ggctcaagcc tgtgcaggaa atcgtgtcag gcgatcagta 660
 ggtagctcat tgtcatgcat aaatcttgat tgggatgtca taagggataa aactaagaca 720
 aagatagagt ctttgaaaga gcatggccct atcaaaaaata aaatgagcga aagtcccaat 780
 aaaacagtat ctgaggaaaa agctaaacaa tacctagaag aatttcattca aacggcatta 840
 gagcatcctg aattgtcaga acttaaaacc gttactggga ccaatcctgt attcgctggg 900
 gctaactatg cggcgtgggc agtaaacgtt gcgcaagtta tcgatagcga aacagctgat 960
 aatttggaag agacaactgc tgctctttcg atacttcctg gtatcggtag cgtaatgggc 1020

```

attgcagacg gtgccgttca ccacaataca gaagagatag tggcacaatc aatagcttta 1080
tcgtctttta tggttgctca agctattcca ttggtaggag agctagttga tattggtttc 1140
gctgcatata attttgtaga gagtattatc aatttatttc aagtagttca taattcgtat 1200
aatcgtcccc cgtattctcc ggggcataaa acgcaaccat ttcttcatga cgggtatgct 1260
gtcagttgga acactgttga agattcgata atccgaactg gttttcaagg ggagagtggg 1320
cacgacataa aaattactgc tgaaaatacc ccgcttccaa tcgcgggtgt cctactaccg 1380
actattcctg gaaagctgga cgtaataaag tccaagactc atatttccgt aaatggtcgg 1440
aaaataagga tgcgttgagc agctatagac ggtgatgtaa ctttttgtcg ccctaaatct 1500
cctgtttatg ttggtaatgg tgtgcatgcy aatcttcacg tggcatttca cagaagcagc 1560
tcggagaaaa ttcattctaa tgaaatttcg tcggattcca taggcgttct tgggtaccag 1620
aaaacagtag atcacaccaa ggtaattctt aagctatcgc tattttttga aatcaaaagc 1680
tga
1683

```

<210> 2

<211> 1566

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:DTGM-L1
DT-GMCSF fusion protein in which native furin
recognition cleavage site replaced by matrix
metalloproteinase (MMP) recognition cleavage site

<400> 2

```

atggggcgccg acgacgtcgt cgactcttct aaatcttttg tgatggaaaa cttttcttcg 60
taccacggga ctaaacctgg ttatgtagat tccattcaaa aaggatataca aaagccaaaa 120
tctggtacac aaggaaatta tgacgatgat tggaaagggg tttatagtac cgacaataaa 180
tacgacgctg cgggatactc tgtagataat gaaaacccgc tctctggaaa agctggaggc 240
gtggtcaaaag tgacgtatcc aggactgacg aaggttctcg cactaaaagt ggataatgcc 300
gaaactatta agaaagagtt aggtttaagt ctactgaac cgttgatgga gcaagtcgga 360
acggaagagt ttatcaaaaag gttcgggtgat ggtgcttcgc gtgtagtgct cagccttccc 420
ttcgctgagg ggagttctag cgttgaatat attaataact gggaaacaggc gaaagcgtaa 480
agcgtagaac ttgagattaa ttttgaaacc cgtggaaaac gtggccaaga tgcgatgtat 540
gagtatatgg ctcaagcctg tgcaggaaat ggaccattag gaatgttgag tcaaggtagc 600
tcattgtcat gcataaatct tgattgggat gtcataaggg ataaaaactaa gacaaaagata 660
gagtctttga aagagcatgg ccctatcaaa aataaaatga gcgaaagtcc caataaaaca 720
gtatctgagg aaaaagctaa acaataccta gaagaatttc atcaaacggc attagagcat 780
cctgaattgt cagaacttaa aaccgttact gttatcgata gcgaaacagc tgataatttg 840
tatgcggcgt gggcagtaaa cgttgcgcaa gttatcgata gcgaaacagc tgataatttg 900
gaaaagacaa ctgctgctct ttcgatactt cctggtatcg gtagegtaat gggcattgca 960
gacggtgccg ttcaccacaa tacagaagag atagtggcac aatcaatagc tttatcgtct 1020
ttaatggttg ctcaagctat tccattggta ggagagctag ttgatatttg tttcgctgca 1080
tataattttg tagagagtat tatcaattta tttcaagtag ttcataattc gtataatcgt 1140
cccgcgtatt ctcccgggca taaaacgagg cctcatatgg caccagcacg atcgccaagc 1200
ccaagcacgc agccctggga gcatgtgaat gccatccagg aggcccgggc tctcctgaac 1260
ctgagtagag acactgctgc tgagatgaat gaaacagtag aagtcattct agaaatgttt 1320
gacctccagg agccgacctg cctacagacc cgcctggagc tgtacaagca gggcctgcgg 1380
ggcagcctca ccaagctcaa gggccocttg accatgatgg ctagccacta caagcagcac 1440
tgccctccaa ccccggaaac ttctgtgctg acccagacta tcacctttga aagtttcaaa 1500
gagaacctga aggactttct gcttgtcatt ccctttgact gctgggagcc agtacaggaa 1560
gcttga
1566

```

<210> 3

<211> 1566

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:DTGM-L2
DT-GMCSF fusion protein in which native furin
recognition cleavage site replaced by matrix
metalloproteinase (MMP) recognition cleavage site

<400> 3

```
atgggcgccg acgacgtcgt cgactcttct aaatcttttg tgatggaaaa cttttcttcg 60
taccacggga ctaaacctgg ttatgtagat tccattcaaa aaggtataca aaagccaaaa 120
tctggtacac aaggaaatta tgacgatgat tggaaagggt tttatagtag cgacaataaa 180
tacgacgctg cgggatactc tgtagataat gaaaacccgc tctctggaaa agctggaggc 240
gtggtcaaag tgacgtatcc aggactgacg aaggttctcg cactaaaagt ggataatgcc 300
gaaactatta agaaagagtt aggtttaagt ctactgaac cgttgatgga gcaagtcgga 360
acggaagagt ttatcaaaag gttcggtgat ggtgcttcgc gtgtagtgct cagccttccc 420
ttcgctgagg ggagttctag cgttgaatat attaataact gggaacaggc gaaagcgta 480
agcgtagaac ttgagattaa ttttgaaacc cgtggaaaac gtggccaaga tgcgatgtat 540
gagtatatgg ctcaagcctg tgcaggaaat ggaccattag gattatgggc acaaggtagc 600
tcattgtcat gcataaatct tgattgggat gtcataaggg ataaaactaa gacaaagata 660
gagtctttga aagagcatgg ccctatcaaa aataaaatga gcgaaagtcc caataaaaca 720
gtatctgagg aaaaagctaa acaataccta gaagaatttc atcaaacggc attagagcat 780
cctgaattgt cagaacttaa aaccgttact gggaccaatc ctgtattcgc tggggctaac 840
tatgcggcgt gggcagtaaa cgttgcgcaa gttatcgata gcgaaacagc tgataatttg 900
gaaaagacaa ctgctgctct ttcgatactt cctggtatcg gtagecgaat gggcattgca 960
gacggtgccg ttaccacaa tacagaagag atagtggcac aatcaatagc tttatcgtct 1020
ttaatggttg ctcaagctat tccattggta ggagagctag ttgatattgg tttcgctgca 1080
tataattttg tagagagtat tatcaattta tttcaagtag ttcataattc gtataatcgt 1140
cccgcgtatt ctcccgggca taaaacgagg cctcatatgg caccagcacg atcgccaagc 1200
ccaagcacgc agccctggga gcatgtgaat gccatccagg aggcccggcg tctcctgaac 1260
ctgagtagag acactgctgc tgagatgaat gaaacagtag aagtcattctc agaaatgttt 1320
gacctccagg agccgacctg cctacagacc cgcctggagc tgtacaagca gggcctgcgg 1380
ggcagcctca ccaagctcaa gggccccttg accatgatgg ctagccacta caagcagcac 1440
tgccctccaa ccccggaaac ttctgtgctg acccagacta tcacctttga aagtttcaaa 1500
gagaacctga aggactttct gcttgtcatc ccctttgact gctgggagcc agtacaggaa 1560
gcttga 1566
```

<210> 4

<211> 1560

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:DTGM-U2 DT-GMCSF fusion
protein in which native furin recognition cleavage site
replaced by urokinase-type plasminogen activator (uPA)
recognition cleavage site

<400> 4

```
atgggcgccg acgacgtcgt cgactcttct aaatcttttg tgatggaaaa cttttcttcg 60
taccacggga ctaaacctgg ttatgtagat tccattcaaa aaggtataca aaagccaaaa 120
tctggtacac aaggaaatta tgacgatgat tggaaagggt tttatagtag cgacaataaa 180
tacgacgctg cgggatactc tgtagataat gaaaacccgc tctctggaaa agctggaggc 240
gtggtcaaag tgacgtatcc aggactgacg aaggttctcg cactaaaagt ggataatgcc 300
gaaactatta agaaagagtt aggtttaagt ctactgaac cgttgatgga gcaagtcgga 360
acggaagagt ttatcaaaag gttcggtgat ggtgcttcgc gtgtagtgct cagccttccc 420
ttcgctgagg ggagttctag cgttgaatat attaataact gggaacaggc gaaagcgta 480
agcgtagaac ttgagattaa ttttgaaacc cgtggaaaac gtggccaaga tgcgatgtat 540
gagtatatgg ctcaagcctg tgcaggaaat ggaagtggaa gatcagcagg tagctcattg 600
tcattgcataa atcttgattg ggatgtcata agggataaaa ctaagacaaa gatagagctc 660
ttgaaagagc atggccctat caaaaataaa atgagcgaaa gtcccaataa aacagtatct 720
gaggaaaaag ctaaacataa cctagaagaa tttcatcaaa cggcattaga gcattcctgaa 780
```

ttgtcagaac	ttaaaaccgt	tactgggacc	aatcctgtat	tcgctggggc	taactatgcg	840
gcgtgggcag	taaacgttgc	gcaagttatc	gatagcgaaa	cagctgataa	tttggaaaag	900
acaactgctg	ctctttcgat	acttcctggg	atcggtagcg	taatgggcat	tgcagacggg	960
gccgttcacc	acaatacaga	agagatagtg	gcacaatcaa	tagctttatc	gtctttaatg	1020
gttgctcaag	ctattccatt	ggtaggagag	ctagttgata	ttggtttcgc	tgcataataat	1080
tttgtagaga	gtattatcaa	tttatttcaa	gtagttcata	attcgtataa	tcgtcccgcg	1140
tattctcccg	ggcataaaaac	gaggcctcat	atggcaccag	cacgatcgcc	aagcccaagc	1200
acgcagccct	gggagcatgt	gaatgccatc	caggaggccc	ggcgtctcct	gaacctgagt	1260
agagacactg	ctgctgagat	gaatgaaaca	gtagaagtca	tctcagaaat	gtttgacctc	1320
caggagccga	cctgcctaca	gacccgcctg	gagctgtaca	agcagggcct	gcggggcagc	1380
ctcaccaagc	tcaagggccc	cttgaccatg	atggctagcc	actacaagca	gcactgccct	1440
ccaaccccgg	aaacttcctg	tgcgaccag	actatcacct	ttgaaagttt	caaagagaac	1500
ctgaaggact	ttctgcttgt	catccccctt	gactgctggg	agccagtaca	ggaagcttga	1560

<210> 5

<211> 1560

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:DTGM-U3 DT-GMCSF fusion protein in which native furin recognition cleavage site replaced by urokinase-type plasminogen activator (uPA) recognition cleavage site

<400> 5

atgggcgccg	acgacgtcgt	cgactcttct	aaatcttttg	tgatggaaaa	cttttcttcg	60
taccacggga	ctaaacctgg	ttatgtagat	tccattcaaa	aaggtataca	aaagccaaaa	120
tctggtagac	aaggaaatta	tgacgatgat	tggaagggt	tttatagtag	cgacaataaa	180
tacgacgctg	cgggatactc	tgtagataat	gaaaaccgcg	tctctggaaa	agctggaggc	240
gtgggtcaaa	tgacgtatcc	aggactgacg	aaggttctcg	cactaaaagt	ggataatgcc	300
gaaactatta	agaaagagtt	aggtttaagt	ctcactgaac	cgttgatgga	gcaagtcgga	360
acggaagagt	ttatcaaaaag	gttcggtgat	ggtgcttcgc	gtgtagtgct	cagccttccc	420
ttcgctgagg	ggagttctag	cgttgaatat	attaataact	gggaacaggc	gaaagcgta	480
agcgtagaac	ttgagattaa	ttttgaaacc	cgtggaaaac	gtggccaaga	tgcgatgtat	540
gagtatatgg	ctcaagcctg	tgcaggaaat	ggaagtggaa	aatcagcagg	tagctcattg	600
tcatgcataa	atcttgattg	ggatgtcata	agggataaaa	ctaagacaaa	gatagagtct	660
ttgaaagagc	atggccctat	caaaaataaa	atgagcgaaa	gtcccaataa	aacagtatct	720
gaggaaaaag	ctaaacaata	cctagaagaa	tttcatcaaa	cggcattaga	gcatacctgaa	780
ttgtcagaac	ttaaaaccgt	tactgggacc	aatcctgtat	tcgctggggc	taactatgcg	840
gcgtgggcag	taaacgttgc	gcaagttatc	gatagcgaaa	cagctgataa	tttggaaaag	900
acaactgctg	ctctttcgat	acttcctggg	atcggtagcg	taatgggcat	tgcagacggg	960
gccgttcacc	acaatacaga	agagatagtg	gcacaatcaa	tagctttatc	gtctttaatg	1020
gttgctcaag	ctattccatt	ggtaggagag	ctagttgata	ttggtttcgc	tgcataataat	1080
tttgtagaga	gtattatcaa	tttatttcaa	gtagttcata	attcgtataa	tcgtcccgcg	1140
tattctcccg	ggcataaaaac	gaggcctcat	atggcaccag	cacgatcgcc	aagcccaagc	1200
acgcagccct	gggagcatgt	gaatgccatc	caggaggccc	ggcgtctcct	gaacctgagt	1260
agagacactg	ctgctgagat	gaatgaaaca	gtagaagtca	tctcagaaat	gtttgacctc	1320
caggagccga	cctgcctaca	gacccgcctg	gagctgtaca	agcagggcct	gcggggcagc	1380
ctcaccaagc	tcaagggccc	cttgaccatg	atggctagcc	actacaagca	gcactgccct	1440
ccaaccccgg	aaacttcctg	tgcgaccag	actatcacct	ttgaaagttt	caaagagaac	1500
ctgaaggact	ttctgcttgt	catccccctt	gactgctggg	agccagtaca	ggaagcttga	1560

<210> 6

<211> 1341

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:DTEGF-L1 DT-EGF
fusion protein in which native furin recognition
cleavage site replaced by matrix metalloproteinase
(MMP) recognition cleavage site

<400> 6

```
atgggcgccg acgacgtcgt cgactcttct aaatcttttg tgatggaaaa cttttcttcg 60
taccacggga ctaaacctgg ttatgtagat tccattcaaa aaggtatata aaagccaaaa 120
tctggtacac aaggaaatta tgacgatgat tggaaagggg tttatagtag cgacaataaa 180
tacgacgctg cgggatactc tgtagataat gaaaaccgcg tctctggaaa agctggaggc 240
gtgggtcaaag tgacgtatcc aggactgacg aaggttctcg cactaaaagt ggataatgcc 300
gaaactatta agaaagagtt aggtttaagt ctactgaac cgttgatgga gcaagtcgga 360
acggaagagt ttatcaaaag gttcgggtgat ggtgcttcgc gtgtagtgct cagccttccc 420
ttcgctgagg ggagttctag cgttgaatat attaataact gggaacaggc gaaagcggtta 480
agcgtagaac ttgagattaa ttttgaaacc cgtggaaaac gtggccaaga tgcgatgtat 540
gagtatatgg ctcaagcctg tgcaggaaat ggaccattag gaatgttgag tcaaggtagc 600
tcattgtcat gcataaatct tgattgggat gtcataaggg ataaaactaa gacaaagata 660
gagtctttga aagagcatgg ccctatcaaa aataaaatga gcgaaagtcc caataaaaca 720
gtatctgagg aaaaagctaa acaataccta gaagaatttc atcaaacggc attagagcat 780
cctgaattgt cagaacttaa aaccgttact gggaccaatc ctgtattcgc tggggctaac 840
tatgcggcgt gggcagtaaa cgttgcgcaa gttatcgata gcgaaacagc tgataatttg 900
gaaaagacaa ctgctgctct ttcgataact cctggtatcg gtacgtaat gggcattgca 960
gacggtgccg ttcaccacaa tacagaagag atagtggcac aatcaatagc tttatcgtct 1020
ttaatggttg ctcaagctat tccattggta ggagagctag ttgatattgg tttcgctgca 1080
tataattttg tagagagtat tatcaattta tttcaagtag ttcataattc gtataatcgt 1140
cccgcgtatt ctcccgggca taaaacgagg cctcatatga attccgatag cgagtgtcct 1200
ctgagtcacg atggttactg tctacatgac ggcgtctgta tgtatattga ggctctagac 1260
aagtacgcgt gtaattgcgt tgttggtac atcgggtgagc gctgtcagta tcgagatctg 1320
aatgggtggg aacttagata a                                     1341
```

<210> 7

<211> 1341

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:DTEGF-L2 DT-EGF
fusion protein in which native furin recognition
cleavage site replaced by matrix metalloproteinase
(MMP) recognition cleavage site

<400> 7

```
atgggcgccg acgacgtcgt cgactcttct aaatcttttg tgatggaaaa cttttcttcg 60
taccacggga ctaaacctgg ttatgtagat tccattcaaa aaggtatata aaagccaaaa 120
tctggtacac aaggaaatta tgacgatgat tggaaagggg tttatagtag cgacaataaa 180
tacgacgctg cgggatactc tgtagataat gaaaaccgcg tctctggaaa agctggaggc 240
gtgggtcaaag tgacgtatcc aggactgacg aaggttctcg cactaaaagt ggataatgcc 300
gaaactatta agaaagagtt aggtttaagt ctactgaac cgttgatgga gcaagtcgga 360
acggaagagt ttatcaaaag gttcgggtgat ggtgcttcgc gtgtagtgct cagccttccc 420
ttcgctgagg ggagttctag cgttgaatat attaataact gggaacaggc gaaagcggtta 480
agcgtagaac ttgagattaa ttttgaaacc cgtggaaaac gtggccaaga tgcgatgtat 540
gagtatatgg ctcaagcctg tgcaggaaat ggaccattag gattatgggc acaaggtagc 600
tcattgtcat gcataaatct tgattgggat gtcataaggg ataaaactaa gacaaagata 660
gagtctttga aagagcatgg ccctatcaaa aataaaatga gcgaaagtcc caataaaaca 720
gtatctgagg aaaaagctaa acaataccta gaagaatttc atcaaacggc attagagcat 780
cctgaattgt cagaacttaa aaccgttact gggaccaatc ctgtattcgc tggggctaac 840
tatgcggcgt gggcagtaaa cgttgcgcaa gttatcgata gcgaaacagc tgataatttg 900
gaaaagacaa ctgctgctct ttcgataact cctggtatcg gtacgtaat gggcattgca 960
gacggtgccg ttcaccacaa tacagaagag atagtggcac aatcaatagc tttatcgtct 1020
```

```

ttaatggttg ctcaagctat tccattggta ggagagctag ttgatattgg tttcgctgca 1080
tataattttg tagagagtat tatcaattta tttcaagtag ttcataattc gtataatcgt 1140
cccgcgtatt ctcccgggca taaaacgagg cctcatatga attccgatag cgagtgtcct 1200
ctgagtcacg atgggttactg tctacatgac ggcgtctgta tgtatattga ggctctagac 1260
aagtacgcgt gtaattgcgt tgttggctac atcggtgagc gctgtcagta tcgagatctg 1320
aatggtggg aacttagata a                                     1341

```

<210> 8

<211> 1335

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DTEGF-U2 DT-EGF fusion protein in which native furin recognition cleavage site replaced by urokinase-type plasminogen activator (uPA) recognition cleavage site

<400> 8

```

atgggcgcgcg acgacgtcgt cgactcttct aaatcttttg tgatggaaaa cttttcttcg 60
taccacggga ctaaacctgg ttatgtagat tccattcaaa aaggtataca aaagccaaaa 120
tctgggtacac aaggaaatta tgacgatgat tggaaaggg tttatagtag cgacaataaa 180
tacgacgctg cgggatactc tgtagataat gaaaaccgc tctctggaaa agctggaggc 240
gtggtcaaag tgacgtatcc aggactgacg aaggttctcg cactaaaagt ggataatgcc 300
gaaactatta agaaagagtt aggtttaagt ctactgaac cgttgatgga gcaagtcgga 360
acggaagagt ttatcaaaaag gttcgggtgat ggtgcttcgc gtgtagtgct cagccttccc 420
ttcgctgagg ggagttctag cgttgaatat attaataact gggaacaggc gaaagcgta 480
agcgtagaac ttgagattaa ttttgaaacc cgtggaaaac gtggccaaga tgcgatgtat 540
gagtatatgg ctcaagcctg tgcaggaaat ggaagtggaa gatcagcagg tagctcattg 600
tcatgcataa atcttgattg ggatgtcata agggataaaa ctaagacaaa gatagagtct 660
ttgaaagagc atggccctat caaaaataaa atgagcgaaa gtccaataa aacagtatct 720
gaggaaaaag ctaaacaata cctagaagaa tttcatcaaa cggcattaga gcatcctgaa 780
ttgtcagaac ttaaaaccgt tactgggacc aatcctgtat tcgctggggc taactatgcg 840
gcgtgggcag taaacgttgc gcaagttatc gatagcgaaa cagctgataa tttggaaaag 900
acaactgctg ctctttcgat acttcctggt atcggtagcg taatgggcat tgcagacggc 960
gccgttcacc acaatacaga agagatagtg gcacaatcaa tagctttatc gtctttaatg 1020
gttgctcaag ctattccatt ggtaggagag ctagttagata ttggtttcgc tgcataataa 1080
ttttagagaa gtattatcaa tttatttcaa gtagttcata attcgtataa tcgtcccgcg 1140
tattctcccg ggcataaaaac gaggcctcat atgaattccg atagcgagtg tcctctgagt 1200
cacgatgggt actgtctaca tgacggcgct tgtatgtata ttgaggctct agacaagtac 1260
gcgtgtgaatt gcgttggttg ctacatcggg gagcgcgtgc agtatcgaga tctgaaatgg 1320
tgggaactta gataa                                     1335

```

<210> 9

<211> 1335

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: DTEGF-U3 DT-EGF fusion protein in which native furin recognition cleavage site replaced by urokinase-type plasminogen activator (uPA) recognition cleavage site

<400> 9

```

atgggcgcgcg acgacgtcgt cgactcttct aaatcttttg tgatggaaaa cttttcttcg 60
taccacggga ctaaacctgg ttatgtagat tccattcaaa aaggtataca aaagccaaaa 120
tctgggtacac aaggaaatta tgacgatgat tggaaaggg tttatagtag cgacaataaa 180
tacgacgctg cgggatactc tgtagataat gaaaaccgc tctctggaaa agctggaggc 240

```

```

gtgggtcaaag tgacgtatcc aggactgacg aagggttctcg cactaaaagt ggataatgcc 300
gaaactatta agaaagagtt aggtttaagt ctactgaac cgttgatgga gcaagtcgga 360
acggaagagt ttatcaaaag gttcgggtgat ggtgcttcgc gtgtagtgtc cagccttccc 420
ttcgctgagg ggagttctag cgttgaatat attaataact gggaacaggc gaaagcggtta 480
agcgtagaac ttgagattaa ttttgaaacc cgtggaaaac gtggccaaga tgcgatgtat 540
gagtatatgg ctcaagcctg tgcaggaaat ggaagtggaa aatcagcagg tagctcattg 600
tcatgcataa atcttgattg ggatgtcata agggataaaa ctaagacaaa gatagagtct 660
ttgaaagagc atggccctat caaaaataaa atgagcgaaa gtcccaataa aacagtatct 720
gaggaaaaag ctaaacaata cctagaagaa tttcatcaaa cggcattaga gcatcctgaa 780
ttgtcagaac ttaaaaccgt tactgggacc aatcctgtat tcgctggggc taactatgcy 840
gcgtgggagc taaacgttgc gcaagttatc gatagcgaaa cagctgataa tttggaaaag 900
acaactgctg ctctttcgtg acttctcgtg atcggtagcg taatgggcat tgcagacggt 960
gccgttcacc acaatacaga agagatagtg gcacaatcaa tagctttatc gtctttaatg 1020
gttgctcaag ctattccatt ggtaggagag ctagttgata ttggtttcgc tgcataataa 1080
ttttagagaga gtattatcaa tttatttcaa gtagttcata attcgtataa tcgtcccgcg 1140
tattctcccg ggcatataaac gaggcctcat atgaattccg atagcgagtg tctctgagt 1200
cacgatgggt actgtctaca tgacggcgctc tgtatgtata ttgaggctct agacaagtac 1260
gcgtgtaatt gcgttggttg ctacatcggt gagcgctgct agtatcgaga tctgaaatgg 1320
tgggaactta gataa 1335

```

<210> 10

<211> 1581

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:DTIL2-L1 DT-IL2
fusion protein in which native furin recognition
cleavage site replaced by matrix metalloproteinase
(MMP) recognition cleavage site

<400> 10

```

atggggcgccg acgacgtcgt cgactcttct aaatcttttg tgatggaaaa cttttcttcg 60
taccacggga ctaaaccctgg ttatgtagat tccattcaaa aaggtataca aaagccaaaa 120
tctggtacac aaggaaatta tgacgatgat tggaaagggg tttatagtac cgacaataaa 180
tacgacgctg cgggatactc tgtagataat gaaaaccgct tctctggaaa agctggaggc 240
gtgggtcaaag tgacgtatcc aggactgacg aagggttctcg cactaaaagt ggataatgcc 300
gaaactatta agaaagagtt aggtttaagt ctactgaac cgttgatgga gcaagtcgga 360
acggaagagt ttatcaaaag gttcgggtgat ggtgcttcgc gtgtagtgtc cagccttccc 420
ttcgctgagg ggagttctag cgttgaatat attaataact gggaacaggc gaaagcggtta 480
agcgtagaac ttgagattaa ttttgaaacc cgtggaaaac gtggccaaga tgcgatgtat 540
gagtatatgg ctcaagcctg tgcaggaaat ggaccattag gaatgttgag tcaaggtagc 600
tcattgtcat gcataaatct tgattgggat gtcataaggg ataaaactaa gacaaagata 660
gagtctttga aagagcatgg ccctatcaaa aataaaatga gcgaaagtcc caataaaaca 720
gtatctgagg aaaaagctaa acaataccta gaagaatttc atcaaacggc attagagcat 780
cctgaattgt cagaacttaa aaccgttact gggaccaatc ctgtattcgc tggggctaac 840
tatgcggcgt gggcagtaaa cgttgcgcaa gttatcgata gcgaaacagc tgataatttg 900
gaaaagacaa ctgctgctct ttcgatactt cctggtatcg gtagcgtaat gggcattgca 960
gacggtgccg ttcaccacaa tacagaagag atagtggcac aatcaatagc tttatcgtct 1020
ttaatgggtg ctcaagctat tccattggta ggagagctag ttgatattgg tttcgctgca 1080
tataattttg tagagagtat tatcaattta tttcaagtag ttcataattc gtataatcgt 1140
cccgcgtatt ctcccgggca taaaacgagg cctcatatgg cacctacttc aagttctaca 1200
aagaaaacac agctacaact ggagcattta ctgctggatt tacagatgat tttgaatgga 1260
attaataatt acaagaatcc caaactcacc aggatgctca catttaagtt ttacatgccc 1320
aagaaggcca cagaactgaa acatcttcag tgtctagaag aagaactcaa acctctggag 1380
gaagtgctaa atttagctca aagcaaaaac tttcacttaa gaccaggga cttaatcagc 1440
aatatcaagc taatagttct ggaactaaag ggatctgaaa caacattcat gtgtgaatat 1500
gctgatgaga cagcaacctt tgtagaattt ctgaacagat ggattacctt ttgtcaaagc 1560
atcatctcaa cactgacttg a 1581

```

<210> 11
 <211> 1581
 <212> DNA
 <213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:DTIL2-L2 DT-IL2
 fusion protein in which native furin recognition
 cleavage site replaced by matrix metalloproteinase
 (MMP) recognition cleavage site

<400> 11

```

atggg'gcgcg acgacgctcg cgactcttct aaatcttttg tgatggaaaa cttttcttcg 60
taccacggga ctaaacctgg ttatgtagat tccattcaaa aaggtataca aaagccaaaa 120
tctggtacac aaggaaatta tgacgatgat tggaaagggt tttatagtac cgacaataaa 180
tacgacgctg cgggatactc tgtagataat gaaaacccgc tctctggaaa agctggaggc 240
gtgggtcaaag tgacgtatcc aggactgacg aaggttctcg cactaaaagt ggataatgcc 300
gaaactatta agaaagagtt aggtttaagt ctcaactgaac cgttgatgga gcaagtcgga 360
acggaagagt ttatcaaaaag gttcgggtgat ggtgcttcgc gtgtagtgct cagccttccc 420
ttcgctgagg ggagttctag cgttgaatat attaataact gggaacaggc gaaagcgta 480
agcgtagaac ttgagattaa ttttgaaacc cgtggaaaac gtggccaaga tgcgatgtat 540
gagtatatgg ctcaagcctg tgcaggaaat ggaccattag gattatgggc acaaggtagc 600
tcattgtcat gcataaatct tgattgggat gtcataaggg ataaaaactaa gacaaagata 660
gagtctttga aagagcatgg ccctatcaaa aataaaatga gcgaaagtcc caataaaaca 720
gtatctgagg aaaaagctaa acaataccta gaagaatttc atcaaacggc attagagcat 780
cctgaattgt cagaacttaa aaccgttact gggaccaatc ctgtattcgc tggggctaac 840
tatgcggcgt gggcagtaaa cgttgcgcaa gttatcgata gcgaaacagc tgataatttg 900
gaaaagacaa ctgctgctct ttcgataact cctgggtatcg gtacgtaat gggcattgca 960
gacggtgccg ttcaccacaa tacagaagag atagtggcac aatcaatagc tttatcgctc 1020
ttaatggttg ctcaagctat tccattggta ggagagctag ttgatattgg tttcgctgca 1080
tataattttg tagagagtat tatcaattta tttcaagtag ttcataattc gtataatcgt 1140
cccgcgattt ctcccgggca taaaacgagg cctcatatgg cacctacttc aagttctaca 1200
aagaaaacac agctacaact ggagcattta ctgctggatt tacagatgat tttgaatgga 1260
attaataatt acaagaatcc caaactcacc aggatgctca catttaagtt ttacatgccc 1320
aagaaggcca cagaactgaa acatcttcag tgtctagaag aagaactcaa acctctggag 1380
gaagtgctaa atttagctca aagcaaaaac tttcacttaa gaccagggga cttaatcagc 1440
aatatcaacg taatagttct ggaactaaag ggatctgaaa caacattcat gtgtgaatat 1500
gctgatgaga cagcaacat tgtagaattt ctgaacagat ggattacctt ttgtcaaagc 1560
atcatctcaa cactgacttg a                                     1581

```

<210> 12
 <211> 1575
 <212> DNA
 <213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:DTIL2-U2 DT-IL2 fusion
 protein in which native furin recognition cleavage site
 replaced by urokinase-type plasminogen activator (uPA)
 recognition cleavage site

<400> 12

```

atggg'gcgcg acgacgctcg cgactcttct aaatcttttg tgatggaaaa cttttcttcg 60
taccacggga ctaaacctgg ttatgtagat tccattcaaa aaggtataca aaagccaaaa 120
tctggtacac aaggaaatta tgacgatgat tggaaagggt tttatagtac cgacaataaa 180
tacgacgctg cgggatactc tgtagataat gaaaacccgc tctctggaaa agctggaggc 240
gtgggtcaaag tgacgtatcc aggactgacg aaggttctcg cactaaaagt ggataatgcc 300
gaaactatta agaaagagtt aggtttaagt ctcaactgaac cgttgatgga gcaagtcgga 360
acggaagagt ttatcaaaaag gttcgggtgat ggtgcttcgc gtgtagtgct cagccttccc 420
ttcgctgagg ggagttctag cgttgaatat attaataact gggaacaggc gaaagcgta 480

```



```

agcgtagaac ttgagattaa ttttgaaacc cgtggaaaac gtggccaaga tgcgatgtat 540
gagtatatgg ctcaagcctg tgcaggaaat ggaagtggaa gatcagcagg tagctcattg 600
tcatgcataa atcttgattg ggatgtcata agggataaaa ctaagacaaa gatagagtct 660
ttgaaagagc atggccctat caaaaataaa atgagcgaaa gtcccaataa aacagtatct 720
gaggaaaaag ctaaacaata cctagaagaa tttcatcaaa cggcattaga gcatcctgaa 780
ttgtcagaac ttaaaaccgt tactgggacc aatcctgtat tcgctggggc taactatgcg 840
gcgtgggcag taaacgttgc gcaagttatc gatagcgaaa cagctgataa tttggaaaag 900
acaactgctg ctctttcgat acttcctggg atcggtagcg taatgggcat tgcagacggt 960
gccgttcacc acaatacaga agagatagtg gcacaatcaa tagctttatc gtctttaatg 1020
gttgctcaag ctattccatt ggtaggagag ctagttgata ttggtttcgc tgcataata 1080
ttttagagaa gtattatcaa tttatttcaa gtagttcata attcgtataa tcgtcccgcg 1140
tattctcccg ggcataaaaac gaggcctcat atggcaccta cttcaagttc taaaagaaa 1200
acacagctac aactggagca tttactgctg gatttacaga tgattttgaa tggaaatta 1260
aattacaaga atcccaaact caccaggatg ctcacattta agttttacat gcccaagaag 1320
gccacagaac tgaaacatct tcagtgtcta gaagaagaac tcaaacctct ggaggaagt 1380
ctaaatttag ctcaaagcaa aaactttcac ttaagacca gggacttaat cagcaatatc 1440
aacgtaatag ttctggaact aaagggatct gaaacaacat tcatgtgtga atatgctgat 1500
gagacagcaa ccattgtaga atttctgaac agatggatta ccttttgtca aagcatcatc 1560
tcaacactga cttga 1575

```

<210> 13

<211> 1575

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:DTIL2-U3 DT-IL2 fusion protein in which native furin recognition cleavage site replaced by urokinase-type plasminogen activator (uPA) recognition cleavage site

<400> 13

```

atgggcgcgcg acgacgtcgt cgactcttct aaatcttttg tgatggaaaa cttttcttcg 60
taccacggga ctaaaccctg ttatgtagat tccattcaaa aaggtatata aaagccaaaa 120
tctggtacac aaggaaatta tgacgatgat tggaaagggt tttatagtac cgacaataaa 180
tacgacgctg cgggatactc tgtagataat gaaaacccgc tctctggaaa agctggaggc 240
gtggtcaaag tgacgtatcc aggactgacg aaggttctcg cactaaaagt ggataatgcc 300
gaaactatta agaaagagtt aggtttaagt ctactgaac cgttgatgga gcaagtcgga 360
acggaagagt ttatcaaaaag gttcgggtgag ggtctaaccg gtgtagtgtc cagccttccc 420
ttcgctgagg ggagttctag cgttgaatat attaataact gggaacaggc gaaagcgtta 480
agcgtagaac ttgagattaa ttttgaaacc cgtggaaaac gtggccaaga tgcgatgtat 540
gagtatatgg ctcaagcctg tgcaggaaat ggaagtggaa aatcagcagg tagctcattg 600
tcatgcataa atcttgattg ggatgtcata agggataaaa ctaagacaaa gatagagtct 660
ttgaaagagc atggccctat caaaaataaa atgagcgaaa gtcccaataa aacagtatct 720
gaggaaaaag ctaaacaata cctagaagaa tttcatcaaa cggcattaga gcatcctgaa 780
ttgtcagaac ttaaaaccgt tactgggacc aatcctgtat tcgctggggc taactatgcg 840
gcgtgggcag taaacgttgc gcaagttatc gatagcgaaa cagctgataa tttggaaaag 900
acaactgctg ctctttcgat acttcctggg atcggtagcg taatgggcat tgcagacggt 960
gccgttcacc acaatacaga agagatagtg gcacaatcaa tagctttatc gtctttaatg 1020
gttgctcaag ctattccatt ggtaggagag ctagttgata ttggtttcgc tgcataata 1080
ttttagagaa gtattatcaa tttatttcaa gtagttcata attcgtataa tcgtcccgcg 1140
tattctcccg ggcataaaaac gaggcctcat atggcaccta cttcaagttc taaaagaaa 1200
acacagctac aactggagca tttactgctg gatttacaga tgattttgaa tggaaatta 1260
aattacaaga atcccaaact caccaggatg ctcacattta agttttacat gcccaagaag 1320
gccacagaac tgaaacatct tcagtgtcta gaagaagaac tcaaacctct ggaggaagt 1380
ctaaatttag ctcaaagcaa aaactttcac ttaagacca gggacttaat cagcaatatc 1440
aacgtaatag ttctggaact aaagggatct gaaacaacat tcatgtgtga atatgctgat 1500
gagacagcaa ccattgtaga atttctgaac agatggatta ccttttgtca aagcatcatc 1560
tcaacactga cttga 1575

```

<210> 14
 <211> 22
 <212> DNA
 <213> Artificial Sequence

 <220>
 <223> Description of Artificial Sequence:universal 5' T7
 promoter primer (5' primer for DT constructs)

 <400> 14
 gtaatacgac tcactatagg gc 22

 <210> 15
 <211> 61
 <212> DNA
 <213> Artificial Sequence

 <220>
 <223> Description of Artificial Sequence:U2 3' mutagenic
 PCR primer for U2 constructs

 <400> 15
 gatttatgca tgacaatgag ctacctgctg atcttccact tccatttcct gcacaggctt 60
 g 61

 <210> 16
 <211> 61
 <212> DNA
 <213> Artificial Sequence

 <220>
 <223> Description of Artificial Sequence:U3 3' mutagenic
 PCR primer for U3 constructs

 <400> 16
 gatttatgca tgacaatgag ctacctgctg attttccact tccatttcct gcacaggctt 60
 g 61

 <210> 17
 <211> 67
 <212> DNA
 <213> Artificial Sequence

 <220>
 <223> Description of Artificial Sequence:L1 3' mutagenic
 PCR primer for L1 constructs

 <400> 17
 gatttatgca tgacaatgag ctaccttgac tcaacattcc taatgggtcca tttcctgcac 60
 aggcttg 67

 <210> 18
 <211> 67
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence:L2 3' mutagenic
 PCR primer for L2 constructs

<400> 18
 gatttatgca tgacaatgag ctaccttggtg cccataatcc taatgggtcca tttcctgcac 60
 aggcttg 67

<210> 19
 <211> 8
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence:matrix
 metalloproteinase (MMP) recognition cleavage site,
 MMP substrate octapeptide for L1 constructs

<400> 19
 Gly Pro Leu Gly Met Leu Ser Gln
 1 5

<210> 20
 <211> 8
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence:matrix
 metalloproteinase (MMP) recognition cleavage site,
 MMP substrate octapeptide for L2 constructs

<400> 20
 Gly Pro Leu Gly Leu Trp Ala Gln
 1 5

<210> 21
 <211> 6
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence:urokinase
 plasminogen activator (uPA) recognition cleavage
 site, uPA favorite sequence, uPA substrate
 hexapeptide for U2 constructs

<400> 21
 Gly Ser Gly Arg Ser Ala
 1 5

<210> 22
 <211> 6
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence:urokinase
 plasminogen activator (uPA) recognition cleavage
 site, uPA favorite sequence, uPA substrate
 hexapeptide for U3 constructs

<400> 22
 Gly Ser Gly Lys Ser Ala
 1 5

<210> 23
 <211> 6
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence:tissue-type
 plasminogen activator (tPA) recognition cleavage
 site, tPA favorite sequence

<400> 23
 Gln Arg Gly Arg Ser Ala
 1 5

<210> 24
 <211> 16
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence:DTGM-WT furin
 sensitive surface loop sequence

<400> 24
 Cys Ala Gly Asn Arg Val Arg Arg Ser Val Gly Ser Ser Leu Ser Cys
 1 5 10 15

<210> 25
 <211> 16
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence:DTGM-U2 surface
 loop sequence cleaved by urokinase-type
 plasminogen activator (uPA)

<400> 25
 Cys Ala Gly Asn Gly Ser Gly Arg Ser Ala Gly Ser Ser Leu Ser Cys
 1 5 10 15

<210> 26
 <211> 16
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence:DTGM-U3 surface
 loop sequence cleaved by urokinase-type
 plasminogen activator (uPA)

<400> 26
 Cys Ala Gly Asn Gly Ser Gly Lys Ser Ala Gly Ser Ser Leu Ser Cys
 1 5 10 15

<210> 27
 <211> 18
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence:DTGM-L1 surface
 loop sequence cleaved by matrix metalloproteinase
 (MMP)

<400> 27
 Cys Ala Gly Asn Gly Pro Leu Gly Met Leu Ser Gln Gly Ser Ser Leu
 1 5 10 15

Ser Cys

<210> 28
 <211> 16
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence:DTGM-Fu surface
 loop sequence cleaved only by furin

<400> 28
 Cys Ala Gly Asn Arg Ala Ala Arg Ser Val Gly Ser Ser Leu Ser Cys
 1 5 10 15

<210> 29
 <211> 9
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence:plasminogen
 activator cleavage site, uPA and tPA physiological
 substrate sequence

<400> 29
 Pro Cys Pro Gly Arg Val Val Gly Gly
 1 5

<210> 30
 <211> 6
 <212> PRT
 <213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:Diphtheria
toxin (DT) cleavage sequence amino acids 163-170

<400> 30

Arg Val Arg Arg Ser Val
1 5